RESEARCH PAPER

A Review on the Antidiabetic Conjugation of Pramlintide and Pumpkin Seeds Using Green-Synthesized Silver Nanoparticles: A Novel Therapeutic Approach

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ABSTRACT

Consequently, the increasing cases of Type 2 Diabetes have necessitated the development of effective and innovative therapeutic interventions, which include the use of pharmaceutical and food-based therapies. Pramlintide is an innovative therapeutic agent that can be used to control cases of Diabetes. It is a human hormone analog, which is used in the adjunctive treatment of Diabetes. It helps in regulating the levels of blood glucose after meals, slows gastric emptying, and enhances the feeling of fullness. These functions of Pramlintide improve glycemic control and metabolic balance, particularly when used in combination with insulin or other antidiabetic drugs. Over the last few years, there has been an increasing interest in functional foods, which have the potential to provide health benefits beyond the normal nutritional effects of food. Among such functional foods, pumpkin seeds have gained significant attention for their potential to provide various health benefits. Pumpkin seeds contain various beneficial components, which include unsaturated fatty acids, dietary fibers, antioxidants, phytosterols, and minerals such as magnesium and zinc. These components have been identified to play a significant role in preventing and managing cases of diabetes. This review article seeks to address the possible benefits that could arise from using pramlintide in association with bioactive compounds found in pumpkin seeds as an alternative therapeutic strategy for managing diabetes. The review also seeks to discuss the possible advantages that could arise from using pramlintide in association with bioactive compounds found in pumpkin seeds, including their possible formulation and delivery methods that could enable the efficient combination of this drug and other plant-based bioactive compounds. Generally, this new trend in pharmaceutical therapy using functional foods could be seen as a new direction in managing diabetes and other metabolic conditions. The possible synergistic effect of pramlintide and other plant-based bioactive compounds could provide a new and alternative approach in managing diabetes and preventing its possible complications.

Keywords: Diabetes mellitus, Pramlintide, Pumpkin seeds, Silver nanoparticles, Green synthesis, Antidiabetic therapy, Hemoglobin.

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1. Introduction

Diabetes mellitus, a metabolic disease, is characterized by hyperglycemia, and the persistence of this hyperglycemia is a result of impaired insulin secretion, insulin action, or both. It is considered to be one of the most important and challenging diseases in the world, and the incidence of diabetes is increasing rapidly, not only in developed but also in developing countries. According to recent epidemiological studies, the global prevalence of diabetes continues to increase, and it is a major contributor to mortality and morbidity worldwide. Diabetes is a chronic metabolic disease that affects the quality of life and leads to various long-term complications, such as cardiovascular diseases, nephropathy, neuropathy, and retinopathy. The available therapies for diabetes management, such as insulin and oral hypoglycemic agents, are not sufficient for controlling hyperglycemia, and this hyperglycemia can be managed to a certain extent. However, these therapies are not sufficient for the proper regulation of carbohydrate metabolism, and this may result in various adverse effects, such as hypoglycemia, gastrointestinal disturbances, and weight gain. Moreover, conventional treatments fail to control postprandial glucose surges, which are of significant importance in the development of diabetic complications (Bergman et al., 2020). Thus, there is an urgent requirement for innovative therapeutic approaches that can control glycemic levels with minimal side effects. With this intention, peptide-based therapeutic approaches have emerged as promising candidates, considering their high specificity and physiological significance. Among such therapeutic peptides, pramlintide, an artificial variant of the hormone amylin, has drawn significant attention. Amylin, a hormone co-secreted with insulin from the pancreas, is of significant importance in the control of postprandial hyperglycemia by reducing gastric emptying, inhibiting glucagon secretion, and inducing satiety (Young, 2005; Riddle et al., 2007). However, in diabetic patients, including type 1 diabetics, the secretion of amylin is significantly reduced, leading to poor control of hyperglycemia (Weyer et al., 2001). Pramlintide was developed to mimic the physiological effects of amylin, which is used as an adjunct to insulin in the treatment of diabetic patients (Pullman et al., 2006; Hoogwerf et al., 2008) Similarly, nanoparticles synthesized through green chemistry methods involving extracts from plants like neem (*Azadirachta indica*) have also gained considerable attention due to their eco-friendly and cost-effective nature. The bioactive compounds in these extracts are used as reducing and stabilizing agents for nanoparticles (Iravani, 2011; Ahmed et al., 2016). These eco-friendly nanoparticles are not only effective as drug delivery agents but also possess other biological activities like antimicrobial and antioxidant activity (Rai et al., 2014; Khalil et al., 2014). With this background, it is safe to conclude that the conjugate system involving pramlintide and pumpkin seed extracts through eco-friendly silver nanoparticles is an innovative approach in the management and treatment of diabetes. This review aims at exploring and understanding the scientific basis and therapeutic potential of this innovative approach in the management and treatment of diabetes.

2. Pramlintide in Diabetes Management (Expanded with Citations)

Pramlintide is a synthetic analog of the naturally occurring hormone amylin, which is co-secreted with insulin from the pancreas in humans. Amylin is an essential hormone in the regulation of glucose levels in the body. For people with diabetes, particularly type 1 and type 2 diabetes of long duration, the secretion of amylin is absent or significantly decreased, leading to an imbalance in glucose metabolism, resulting in hyperglycemia (Young, 2005; Weyer et al., 2001). The development of pramlintide was intended to replace the physiological effects of amylin in order to control blood glucose levels in patients with diabetes who are on insulin therapy (Riddle et al., 2007; Pullman et al., 2006).

2.1 Pharmacological Role of Pramlintide

Pramlintide works through several pathways that enhance insulin activity. This is a more comprehensive approach to glucose management. One of the ways that pramlintide works is through slowing gastric emptying. This slows the rate at which glucose is introduced into the system. This helps to prevent sudden surges in postprandial glucose levels. These surges are a major cause of complications in diabetes (Hoogwerf et al., 2008; Fineman et al., 2002). Pramlintide also inhibits the production of glucagon. This is a hormone that is known to increase glucose levels in the system. for diabetic patients, the unregulated secretion of glucagon after meals is one of the major factors in hyperglycemia. Pramlintide, by reducing the secretion of glucagon, decreases the hepatic glucose output and hence improves glycemic control (Weyer et al., 2001; Ratner et al., 2004). Another significant pharmacological effect of pramlintide is its capacity to induce satiety and hence reduce food intake. This is particularly significant in patients with type 2 diabetes,

who often present with coexisting obesity and weight problems. The appetite suppressant properties of pramlintide also help in weight loss (Apovian et al., 2015; Hollander et al., 2003).

2.2 Clinical Applications in Diabetes

Pramlintide is indicated for the adjunctive treatment of type 1 and insulin-treated type 2 diabetes patients who are unable to control blood glucose levels with insulin alone. Clinical studies have confirmed that pramlintide helps in the control of blood glucose levels and the improvement of overall glycemic control when used in conjunction with insulin. The studies also showed that the HbA1c levels were reduced when pramlintide was used. In addition, the use of pramlintide was found to result in weight loss. This is an advantage over the conventional drugs that are used in the control of diabetes and that can lead to weight gain. Additionally, emerging studies have shown that pramlintide may have other pharmacological benefits. For example, it was shown that pramlintide may have a protective effect against oxidative stress and endothelial dysfunction, which are considered to be significant factors in the development of vascular complications in diabetes. In addition, there are studies that have shown that pramlintide may be used as a part of cancer therapy, where it may have a synergistic effect in combination with conventional chemotherapy.

2.3 Limitations and Side Effects

Although the therapeutic benefits of pramlintide are significant, its clinical use is also accompanied by certain limitations that make its use challenging and restricted. One of the major challenges in the use of pramlintide is its method of administration, which is injectable and requires multiple subcutaneous injections throughout the day, making it difficult for patients to adhere to the drug (Kommera et al., 2024; Brayden and Maher, 2017). Another limitation of pramlintide is the side effects of the drug, which manifest during the initial stages of drug administration. The most common side effects of pramlintide include nausea, vomiting, and appetite suppression, which make it difficult for patients to adhere to the drug (Pullman et al., 2006; Singh-Franco et al., 2011). Another side effect of pramlintide is hypoglycemia, which is more likely to manifest when the drug is co-administered with insulin, which also lowers blood glucose levels (Ratner et al., 2004). Another side effect of pramlintide is fatigue dizziness, and reduced levels of hemoglobin, which may further complicate diabetes. The effect of pramlintide on hematologic parameters, including levels of hemoglobin, is of particular concern in diabetes patients, as they are prone to anemia (Apovian et al., 2015). Another important issue that poses a significant challenge in the clinical use of pramlintide is the inherent instability of peptides. Peptides are prone to proteolytic cleavage and have poor oral bioavailability, making them difficult to administer orally and necessitating parenteral administration (Fosgerau and Hoffmann, 2015; Patel et al., 2022). Such limitations emphasize the need for the development of drug delivery systems that can improve the efficacy of pramlintide.

2.4 Need for Improved Formulations

In view of the limitations of conventional pramlintide therapy, there is a need for the development of improved formulations that can increase the efficacy of this drug and reduce the occurrence of side effects. In this regard, the use of drug delivery technologies, especially nanotechnology, may help overcome the limitations of conventional pramlintide therapy. In fact, nanotechnology-based drug delivery systems have shown promise in increasing the efficacy of peptides, such as pramlintide, and reducing the occurrence of side effects. In this regard, the conjugation of pramlintide with natural bioactive compounds, such as pumpkin seed extract, may be a promising approach for the development of improved formulations of this drug. Such combination therapies may help increase the efficacy of this drug and reduce the occurrence of side effects, as the natural compounds may help overcome the limitations of conventional pramlintide therapy. In addition, the use of green-synthesized silver nanoparticles as a drug-delivery agent may help increase the efficacy of this drug. In this regard, the conjugation of pramlintide with natural compounds, such as nutraceuticals, and nanotechnology-based drug delivery may be a promising approach for the development of improved formulations of this drug. Such improved formulations may help to mitigate the side effects of the synthetic drug and at the same time increase its efficacy. Moreover, the employment of green synthesized silver nanoparticles as a binding and delivery agent for the drug is likely to increase its stability and delivery (Iravani, 2011; Ahmed et al., 2016). Therefore, it is safe to conclude that the integration of pramlintide with nutraceuticals and nanotechnology is likely to be a promising approach for the development of next-generation anti-diabetic therapies that are effective, safe, and patient-friendly.

3. Pumpkin Seeds (*Cucurbita pepo*) in Diabetes Management

Natural plant-based therapies have received significant attention in recent years as complementary therapies in

the management of chronic diseases such as diabetes mellitus. Among the numerous nutraceuticals, pumpkin seeds (Cucurbita pepo) have emerged as a potential dietary constituent in the management of diabetes mellitus owing to their nutritional and pharmacological properties. Pumpkin seeds are commonly used and are documented to exert significant health benefits, especially in the management of metabolic disorders such as diabetes (Patel, 2013; Sharma et al., 2020). The use of pumpkin seeds in the management of diabetes mellitus is a natural, safe, and effective therapeutic strategy in the management of diabetes mellitus and its complications.

3.1 Nutritional and Phytochemical Composition

Pumpkin seeds are rich in nutrients and phytochemicals that make them beneficial in the prevention and management of diabetes. Pumpkin seeds are rich in various nutrients such as magnesium, zinc, and iron. In addition to these nutrients, pumpkin seeds are rich in protein, dietary fiber, and healthy fats such as polyunsaturated fatty acids. Magnesium is an important mineral that plays a critical role in glucose and insulin metabolism. Magnesium deficiency has been linked with insulin resistance and poor glycemic control in diabetic patients. Magnesium is important in the prevention and management of diabetes because it helps in the improvement of insulin sensitivity. In addition to these nutrients, pumpkin seeds are rich in various phytochemicals such as flavonoids, phenolic acids, tannins, and phytosterols. Phytochemicals in pumpkin seeds have been reported to have antioxidant and anti-inflammatory activities. Phytochemicals in pumpkin seeds are important in the prevention and management of diabetes because they have the ability to scavenge free radicals that are responsible for the development of the disease.

3.2 Antidiabetic and Hypoglycemic Effects

The hypoglycemic effects of pumpkin seeds and extracts have been proven in various experimental and clinical studies. The antidiabetic effects of pumpkin seeds are mainly due to the improvement of insulin sensitivity and the enhancement of glucose uptake in the periphery. Pumpkin polysaccharides were found to decrease blood glucose levels by regulating the metabolism of carbohydrates and improving the functions of pancreatic cells. Pumpkin seeds were also found to have low glycemic index values. The low glycemic index helps in maintaining the blood glucose levels after meals. This is very important in controlling hyperglycemia after meals. Hyperglycemia is one of the factors that cause diabetes. Pumpkin seeds were also found to have healthy fats. The healthy fats in pumpkin seeds are polyunsaturated fatty acids. The healthy fats improve lipid metabolism and insulin sensitivity. Pumpkin seeds were also found to inhibit the activities of enzymes that take part in the digestion of carbohydrates. The enzymes that were inhibited were α-amylase and α-glucosidase. The inhibition of these enzymes slows the absorption of glucose in the body. The slowing of the absorption of glucose in the body helps in preventing sudden spikes in blood glucose levels.

3.3 Antioxidant and Protective Effects

Oxidative stress plays a central role in the development and progression of diabetes and its complications. Chronic hyperglycemia leads to the generation of reactive oxygen species (ROS), which cause cellular damage and impair normal physiological functions. Pumpkin seeds possess strong antioxidant properties due to the presence of phenolic compounds, flavonoids, and vitamins, which help combat oxidative stress (Kim *et al.*, 2012; Nawirska-Olszanska *et al.*, 2013). The antioxidant activity of pumpkin seeds not only protects pancreatic β-cells from oxidative damage but also improves insulin secretion and sensitivity. Additionally, these bioactive compounds exhibit anti-inflammatory effects, which further contribute to their protective role in diabetes management (Amin and Thakur, 2013). Moreover, pumpkin seed oil has been shown to reduce lipid peroxidation and improve antioxidant enzyme activity in diabetic models, thereby preventing complications such as cardiovascular diseases (Makni *et al.*, 2008). These findings emphasize the importance of pumpkin seeds in reducing the oxidative burden associated with diabetes.

3.4 Role in Hemoglobin Improvement and Nutritional Support

One of the significant advantages of pumpkin seeds is their iron content, which is essential in the development of hemoglobin in the body. Iron is often in short supply in diabetic patients, especially those with chronic inflammation or malnutrition. Pumpkin seeds can, therefore, be used to improve iron levels in the body, thus reducing anemia in diabetic patients (Oloyede, 2012). Iron is not the only essential component in pumpkin seeds, as they also contain zinc, which improves the immune system for better insulin function. Zinc is also known to be an essential element in insulin storage, secretion, and action. Therefore, zinc is an essential micronutrient in diabetes management (Glew et al., 2008). The co-existence of iron, zinc, and other micronutrients is beneficial in improving the nutritional status of individuals. Moreover, pumpkin seeds have high levels of dietary fiber that assist in

slowing down glucose absorption. This is beneficial in improving digestion in diabetes patients. The slowing down of glucose absorption also reduces the complications that may occur in diabetes patients (Yadav et al., 2010). Therefore, pumpkin seeds act both as a therapy and a nutritional supplement in diabetes management.

3.5 Therapeutic Potential in Combination Therapy

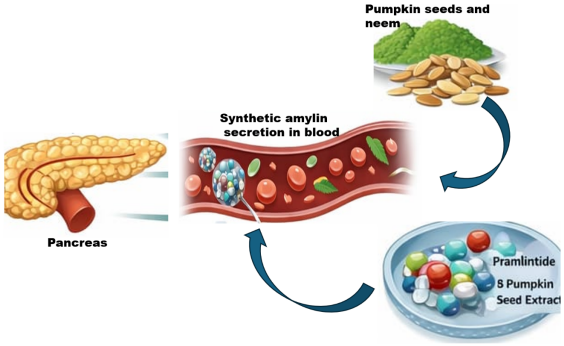

Figure 1: Targeted Drug Delivery System

Pumpkin seeds, in conjunction with conventional anti-diabetic agents, have tremendous therapeutic potential in improving the therapeutic response. Pumpkin seeds, being derived from natural sources and having low toxicity, can be administered in combination without causing significant adverse effects. The ability of pumpkin seeds to increase insulin sensitivity, reduce oxidative stress, and increase hemoglobin levels makes it an ideal adjunct in conjunction with other conventional anti-diabetic agents like pramlintide. In this study, the conjugation of pumpkin seed extract with pramlintide is aimed at achieving a synergistic effect whereby the natural compounds in pumpkin seeds reduce the adverse effects of the drug and increase its therapeutic potential. For example, the iron content in pumpkin seeds might mitigate the decrease in hemoglobin levels that pramlintide treatment entails. The antioxidant activity in pumpkin seeds might also minimize the oxidative stress that the drugs cause. Furthermore, the application of pumpkin seeds in nanotechnology-based drug delivery systems such as silver nanoparticles might maximize the efficacy and bioavailability of the drugs. This new approach in the development of multifunctional drugs for the treatment of diabetes mellitus is innovative in that it combines the therapeutic effects of drugs, nutraceuticals, and nanotechnology.

4. Green Synthesis of Silver Nanoparticles (AgNPs) and Their Role in Drug Delivery (Expanded with Citations)

Nanotechnology has dramatically changed the face of the modern pharmaceutical sciences, and it has provided a new platform for solving the problems of drug delivery, diagnosis, and therapy. Among all the nanoparticles, silver nanoparticles (AgNPs) have shown significant promise for various applications, especially in drug delivery, due to their unique physicochemical properties, such as a high surface area-to-volume ratio, reactivity, and biological compatibility. Therefore, silver nanoparticles are highly promising for drug delivery, especially for treating diseases such as diabetes (Khan et al., 2019; Kumar et al., 2021). In this context, the conventional synthesis of nanoparticles, especially silver nanoparticles, involves the use of toxic reagents and requires a high-temperature reaction. However, in recent times, scientists have focused on the eco-friendly and sustainable synthesis of nanoparticles, also known as green synthesis. In this technique, plant extracts, microbes, or biomolecules are used as reducing agents, replacing conventional reagents. The use of this technique not only minimizes the environmental impact of silver nanoparticles but also enhances the biological activity of the nanoparticles, as the phytochemicals are used as a capping agent.

4.1 Importance of Nanotechnology in Antidiabetic Therapy

Nanotechnology-based drug delivery systems offer several advantages over conventional formulations, particularly for peptide drugs such as pramlintide. One of the primary challenges in peptide therapy is poor stability and rapid degradation in the biological environment. Nanoparticles can encapsulate or bind peptide molecules, protecting them from enzymatic degradation and improving their half-life (Patra *et al.*, 2018; Patel *et al.*, 2022). Additionally, nanocarriers enable controlled and sustained drug release, which helps maintain optimal drug concentrations in the bloodstream and reduces the frequency of administration. This is particularly beneficial for pramlintide, which currently requires multiple daily injections (Kommera *et al.*, 2024). By enhancing bioavailability and reducing dosing frequency, nanotechnology significantly improves patient compliance. Furthermore, nanoparticles can facilitate targeted drug delivery, ensuring that the therapeutic agent reaches specific tissues or cells, thereby minimizing off-target effects and toxicity (Kesharwani *et al.*, 2023). In the context of diabetes, such targeted delivery systems can improve glucose regulation while reducing systemic side effects. Importance of Nanotechnology in Antidiabetic Therapy

Nanotechnology-based drug delivery systems have shown promise over traditional drug delivery systems, especially in the case of peptide drugs such as pramlintide. One of the major problems associated with

the therapeutic use of peptides is their instability and susceptibility to rapid degradation in the biological environment. Nanoparticles can bind to the drug molecules and protect them from enzymatic degradation, thus increasing their half-life (Patra et al., 2018; Patel et al., 2022). Moreover, nanoparticles can be used to achieve controlled and sustained release of the drug, which is essential in maintaining optimal drug concentrations in the blood and reducing the dosing frequency. This is especially true in the case of pramlintide, which is given multiple times a day (Kommera et al., 2024). The use of nanoparticles in drug delivery is also expected to improve the bioavailability of the drug and reduce the dosing frequency, thus making the drug more acceptable to patients. Moreover, nanoparticles can be used to target the drug molecules, which is expected to minimize side effects and toxicity (Kesharwani et al., 2023).

4.2 Green Synthesis of Silver Nanoparticles Using Neem Extract

Green synthesis of silver nanoparticles involves the use of plant extracts as reducing and stabilizing agents. Neem, *Azadirachta indica*, is one of the most commonly used plants for the synthesis of silver nanoparticles. This is because of the presence of a number of phytochemicals, such as flavonoids, terpenoids, phenolic compounds, and tannins, in neem leaves (Khalil et al., 2014). The phytochemicals are involved in the reduction of silver ions to silver nanoparticles. The general process of synthesizing AgNPs by the green method involves the addition of neem leaf extract to an aqueous solution of AgNO3. When the two solutions are mixed, there is a visual change in color from colorless to yellow or brown, which is an indication of the formation of AgNPs due to surface plasmon resonance (Ahmed et al., 2016; Shankar et al., 2004). The AgNPs can then be purified by centrifugation, followed by drying for use in various applications. The advantages of using the green method for synthesizing AgNPs include ease of use, cost-effectiveness, and safety for the environment. Additionally, the use of phytochemicals in the neem leaf extract acts as a capping agent, which enhances the stability of AgNPs (Iravani, 2011) for use in biomedical applications.

4.3 Biological and Pharmacological Properties of AgNPs

AgNPs have been reported to exhibit numerous biological activities that make them valuable in therapy. Some of the biological properties of AgNPs include antimicrobial activity, which makes them effective in preventing infections. AgNPs have been reported to be effective in improving the safety of pharmaceutical formulations (Rai et al., 2014; Das et al., 2017). Apart from antimicrobial activity, AgNPs have been reported to have antioxidant properties. The antioxidant properties of AgNPs make them effective in reducing oxidative stress, which is associated with diabetes. Oxidative stress is reported to be one of the major complications that affect patients with diabetes. Therefore, AgNPs having the ability to reduce oxidative stress make them valuable in therapy. Recently, AgNPs have been reported to have the potential in modulating glucose metabolism, making them effective in antidiabetic therapy (Jini and Sharmila, 2020). AgNPs have also been reported to be effective in enhancing the stability of bioactive compounds, making them valuable in conjugation with drugs.

4.4 Role of AgNPs as a Binding and Drug Delivery Agent

The proposed formulation utilizes AgNPs as a binding agent to conjugate pramlintide with pumpkin seed extract. AgNPs have a high surface area, which enables the adsorption of both peptide drugs and pumpkin seed bioactive components, thus creating a conjugated system (Singh et al., 2018). AgNPs can adsorb both peptide drugs and pumpkin seed bioactive components, thus creating a conjugated system. This conjugated system can improve the stability of the drug, pramlintide, as well as the bioavailability of pumpkin seed components. The nanoparticle delivery system can control the release of the drug components, thus maintaining their efficacy for an extended period (Kumar et al., 2020). AgNPs can improve the permeability of cell membranes, thus enhancing the absorption of the drug. This can be beneficial in developing alternative delivery routes, such as oral delivery, which is currently not feasible due to the instability of the drug in the GI tract (Brayden and Maher, 2017).

4.5 Safety Considerations and Challenges

Though there are numerous advantages of silver nanoparticles, there are certain safety considerations that need to be taken into account for the use of silver nanoparticles in biomedical applications. High concentration of AgNPs may induce cytotoxicity, and this may be attributed to the generation of reactive oxygen species and interactions with cell components (Sharma et al., 2009). Therefore, optimization of size, concentration, and dosage of nanoparticles is a prerequisite for ensuring the safety of the nanoparticles. It has also been reported that green synthesized nanoparticles are safe for use compared to

chemically synthesized nanoparticles, as there are no reports of the use of toxic reagents and the presence of natural capping agents (Kharissova et al., 2013). However, detailed studies on the toxicity of nanoparticles need to be carried out. Another challenge that needs to be addressed for the successful use of nanoparticles in biomedical applications is standardization of the synthesis of nanoparticles, as the composition of plant extracts may vary.

4.6 Relevance to the Proposed Conjugated System

The use of green-synthesized AgNPs in the conjugated system of pramlintide with pumpkin seed is a new, multifaceted approach to managing diabetes. AgNPs, aside from their use as a binding agent, improve the stability, bioavailability, and efficacy of the drug formulation. The AgNPs, by assisting in the controlled release of pramlintide and pumpkin seed bioactive components, contribute to better glycemic control with fewer side effects. Moreover, the antioxidant and antimicrobial activities of AgNPs make them an advantage, which can improve the efficacy of the drug formulation. Thus, the use of green-synthesized AgNPs is a significant component in the development of an advanced drug delivery system for the treatment of diabetes, which utilizes the advantages of nanotechnology, nutraceuticals, and peptide drugs.

5. Methodology of the Pramlintide–Pumpkin Seed Conjugated Formulation

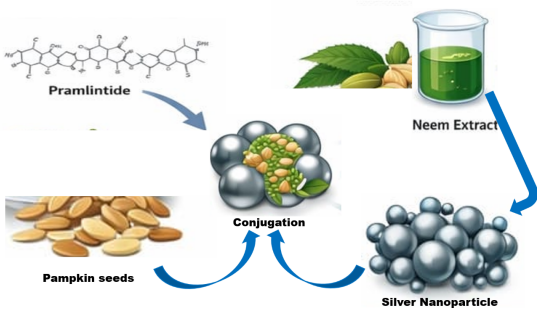

Figure 2: Pramlintide- Pumpkin Seed Silver Nanoparticles Conjugate for Antidiabetic Therapy

The development of a pramlintide–pumpkin seed conjugated system using green synthesized silver nanoparticles is an experimental approach that combines aspects of pharmaceutical formulation, nanotechnology, and green chemistry. The approach is aimed at effectively conjugating synthetic peptide-based drugs with bioactive compounds of natural origin. Each step in the formulation of conjugated systems is significant in creating an effective antidiabetic drug delivery system.

5.1 Preparation of Pumpkin Seed Extract

The first step in the formulation is the preparation of pumpkin seed extract, which acts as the natural bioactive agent in the system. Fresh pumpkin seeds belonging to the species Cucurbita pepo are collected, properly washed to eliminate contaminants, and then dried in the open sun for about 48 hours. This drying step is used to minimize moisture content in the seeds and prevent microbial action on the bioactive agents, thereby maintaining their stability (Yadav et al., 2010). The dried seeds are then crushed into fine powder using a mechanical grinder. This powder contains essential nutrients such as magnesium, zinc, iron, polyunsaturated fatty acids, and antioxidants, which contribute to the antidiabetic effects of the drug (Glew et al., 2006; Patel, 2013). For the purpose of extracting the bioactive components, the powdered seeds can be extracted using solvents such as aqueous or alcoholic solutions. The extracted solution can be filtered and stored in a controlled environment. The polysaccharides, phenolic, and flavonoid components of the solution play an important role in improving insulin sensitivity (Adams et al., 2011; Sharma et al., 2020).

5.2 Incorporation of Pramlintide

Pramlintide, being a peptide drug, should be handled with caution to avoid any kind of degradation, which could affect its biological activity. The drug is incorporated into the prepared pumpkin seed extract in specific conditions. For this purpose, a mixture of nitric acid (10%) and acetic acid (1%) is used to facilitate the dissolution of the drug and the pumpkin seed components, which could interact with the drug. These acidic conditions would allow the drug to interact with the pumpkin seed components, thus enabling their interaction. The mixture is stirred continuously with the help of a magnetic stirrer to facilitate the complete dissolution of the drug. This step is important because, through this process, a preliminary complex of pramlintide with the bioactive components of pumpkin seeds would form, which could increase the stability of the drug.

Table 1: Comparative Roles of Components in the Conjugated System

Component	Source	Key Bioactive Properties	Mechanism of Action	Therapeutic Benefit
Pramlintide	Synthetic peptide (amylin analogue)	Regulates postprandial glucose	Slows gastric emptying, suppresses	Controls blood glucose levels, reduces HbA1c

			glucagon, increases satiety	
Pumpkin Seed Extract (*Cucurbita pepo*)	Natural nutraceutical	Rich in magnesium, zinc, iron, antioxidants	Improves insulin sensitivity, reduces oxidative stress	Enhances glycemic control, improves hemoglobin
Silver Nanoparticles (AgNPs)	Green synthesis (neem extract)	High surface area, antioxidant, antimicrobial	Enhances drug stability and delivery	Improves bioavailability and controlled release

5.3 Green Synthesis of Silver Nanoparticles (AgNPs)

The synthesis of silver nanoparticles is done through the green synthesis method using an aqueous solution of neem leaf extract. Freshly collected neem leaves are washed thoroughly and boiled in distilled water to obtain an aqueous solution containing various phytochemicals such as flavonoids, tannins, and terpenoids (Khalil et al., 2014). This aqueous solution of neem is mixed with an aqueous solution of silver nitrate (AgNO3). In this process, phytochemicals act as reducing agents for silver ions (Ag+) to form metallic silver nanoparticles (Ag0) (Ahmed et al., 2016; Shankar et al., 2004). This chemical reaction is indicated by a color change in the solution from colorless to yellow or brown, which indicates the formation of silver nanoparticles. The silver nanoparticles are then purified by centrifugation and are dried in powder form. This method of silver nanoparticle synthesis is known as green synthesis due to its eco-friendly nature, cost-effectiveness, and biocompatibility of the process (Iravani, 2011).

5.4 Conjugation Using Silver Nanoparticles as Binding Agent

The purified silver nanoparticles are used in the conjugation of the drug with the pramlintide-pumpkin seed mixture, in which the silver nanoparticles are used as a binding agent. The mixture is again subjected to magnetic stirring to allow for the conjugation of the drug with the pumpkin seed bioactive using the silver nanoparticles. The conjugation of the drug with the use of silver nanoparticles is due to their high surface area, which enables them to adsorb both the peptide drug molecule and the phytochemicals, thus forming a conjugated complex (Singh et al., 2018). The conjugation of the drug with the use of silver nanoparticles enhances the stability of the drug by preventing it from undergoing enzymatic degradation, thus increasing the bioavailability of the pumpkin seed bioactive. The conjugation of the drug with the use of silver nanoparticles also enables the drug to be released slowly, thus increasing the therapeutic efficacy of the drug (Patra et al., 2018; Kumar et al., 2021).

5.5 Formulation into Final Dosage Form

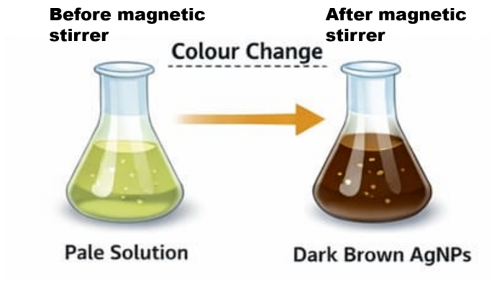

Figure 3: Colour Change of Silver Nanoparticles

The final conjugated product can be formulated into various dosage forms such as tablets or injectable preparations. The formulation of the conjugated product into tablet form can be carried out by drying and compressing the conjugated mixture with the aid of appropriate excipients. The formulation can be made in liquid form for injectable preparations. The injectable route is the standard route for the administration of pramlintide. However, the introduction of nanoparticles into the formulation may provide an opportunity for the development of alternative routes of administration such as the oral and transdermal routes. The introduction of nanoparticles into the formulation is likely to improve the stability and absorption of the drugs. The formulation route is important in the evaluation of the efficacy of the drugs. The development of the tablet formulation of the conjugated product will be a breakthrough in the treatment of diabetes with pramlintide. The tablet formulation will be important in the improvement of patient compliance and the efficacy of the drugs.

5.6 Evaluation and Characterization of the Formulation

Evaluation is essential for assessing the quality, safety, and efficacy of the formulation. The parameters that

need to be evaluated for characterizing the formulation include:

- Particle size and shape: This is evaluated through scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques.
- Zeta potential: This is used to assess the stability of nanoparticles.
- Drug loading and encapsulation efficiency: This is used to assess the amount of pramlintide in the formulation.
- *In vitro* drug release studies: The release profile of the drug under simulated physiological conditions is tested.
- Antidiabetic activity assays: The evaluation includes glucose uptake and enzyme inhibition.
- Toxicity studies: The biocompatibility and safety of the formulation are tested.

The above tests are important in optimizing the formulation and making it appropriate for clinical application. (Kesharwani et al., 2023; Kumar et al., 2020).

5.7 Significance of the Methodology

The methodology discussed above encompasses different highly sophisticated approaches, such as nutraceutical formulation, peptide drug delivery, and green nanotechnology. Such an approach is likely to improve the therapeutic activity of the final product by incorporating the advantages of each compound. The pumpkin seed extract is likely to provide natural antidiabetic and hematological activities, whereas pramlintide is likely to provide effective glycemic control. The green synthesis of silver nanoparticles is likely to improve the stability, bioavailability, and drug release of the final product. Such an approach is likely to be novel and eco-friendly in the formulation of future antidiabetic agents.

6. Mechanism of Action of the Pramlintide–Pumpkin Seed–AgNP Conjugated System

Pramlintide-pumpkin seed conjugated system coupled with green synthesized silver nanoparticles (AgNPs) is a multifaceted therapeutic agent that is aimed at targeting different facets of diabetes mellitus. This is in contrast to conventional monotherapy approaches that only focus on a single therapeutic approach. The pramlintide-pumpkin seed conjugated system coupled with silver nanoparticles is expected to provide synergistic benefits for the management of diabetes mellitus. The mechanism of action is multifaceted and is expected to provide benefits for improving glycemic regulation, oxidative stress, and hematologic parameters.

6.1 Role of Pramlintide in Glycemic Regulation

Pramlintide, being the analogue of amylin, a hormone that helps regulate blood glucose levels, helps regulate blood glucose levels. The deficiency of amylin, as observed in diabetes, results in rapid emptying of the stomach, hyperglucagonemia, and impaired satiety, all of which result in hyperglycemia. In the conjugate system, the role of pramlintide in the regulation of hyperglycemia in diabetes results from the action of the drug, which works primarily through three mechanisms. The drug slows down the rate of emptying of the stomach, resulting in a reduction in the rate of entry of glucose into the blood. The drug also suppresses inappropriate glucagon, resulting in a reduction of hyperglycemia. The drug also enhances satiety, resulting in a reduction of food intake and a resultant reduction of hyperglycemia, especially in type 2 diabetes. The role of pramlintide in the regulation of hyperglycemia in diabetes results from the action of the drug, which works primarily through these mechanisms, and this makes the drug very effective in the management of diabetes.

6.2 Contribution of Pumpkin Seed Bioactives

Pumpkin seed extract makes a significant contribution to the therapeutic effectiveness of the conjugate system through its nutrient and phytochemical composition. The presence of magnesium improves the activity of the insulin receptor and makes the body more sensitive to insulin, which in turn enables glucose uptake in the cells (Glew et al., 2008). The presence of zinc is also significant in the synthesis, storage, and secretion of insulin, which also plays an important role in glucose metabolism. Moreover, the presence of pumpkin seed polysaccharides has also been reported to stimulate pancreatic β-cell function and improve insulin secretion, which plays an essential role in the normalization of glucose metabolism (Adams et al., 2011; Fu et al., 2006). The low glycemic properties of pumpkin seeds ensure the slow release of glucose into the blood, which in turn ensures that the level of glucose in the blood remains normal (Makni et al., 2008) The second significant mechanism is the antioxidant property of pumpkin seeds. The bioactive constituents of pumpkin seed extract, such as flavonoids and phenolic acids, scavenge ROS, thus reducing oxidative stress, which is a key factor in the development of complications in diabetes (Kim et al., 2012; Sharma et al., 2020). This property of pumpkin seed extract would be beneficial in maintaining the function of the pancreas, thus maintaining metabolic

well-being in diabetics. Moreover, the iron content in pumpkin seeds would be beneficial in the production of hemoglobin, thus reducing anemia in diabetics (Oloyede, 2012), which can be a complication of pramlintide use.

6.3 Role of Silver Nanoparticles (AgNPs)

Silver nanoparticles are instrumental in improving the delivery and effectiveness of the conjugate system. The nanoparticles' large surface area and reactivity make them excellent drug carriers that aid in the binding of pramlintide and pumpkin seed bioactives (Singh et al., 2018). One of the significant roles of AgNPs is the stabilization of pramlintide against enzymatic degradation. Peptide drugs are highly prone to degradation in the body, which affects their bioavailability (Patel et al., 2022). The AgNP-carried pramlintide is more likely to maintain its native structure and protect it from degrading enzymes (Patra et al., 2018). The AgNP-carried pramlintide is also more likely to be released in a controlled and sustained manner, ensuring the drug's therapeutic effect is maintained over time (Kumar et al., 2021). The nanoparticles also aid in the improved uptake of pramlintide and its permeability in the body, which might be helpful in finding alternative routes of administration, such as oral administration (Brayden and Maher, 2017). The AgNP also has inherent antioxidant and antimicrobial properties, which make it more effective in delivering therapeutic benefits (Rai et al., 2014; Prabhu et al., 2018). The AgNP's antioxidant properties will complement the inherent antioxidant properties of These also play a role in the therapeutic effects of the formulation. The capacity of these compounds to combat oxidative stress also complements the antioxidant properties of pumpkin seed bioactive compounds, which is a synergistic mechanism of protection (Rai et al., 2014; Prabhu et al., 2018).

6.4 Synergistic Interaction of Components

The interaction of pramlintide, pumpkin seed extract, and silver nanoparticles produces a synergistic effect. Pramlintide is used to treat diabetes by regulating postprandial glucose levels. On the other hand, pumpkin seed bioactive compounds are known to improve insulin sensitivity, provide antioxidant properties, and support hemoglobin synthesis. Therefore, the interaction of these compounds produces an efficient effect. In addition, the presence of silver nanoparticles guarantees efficient delivery of these compounds, ensuring maximum therapeutic potential. This interaction is efficient in treating diabetes because it addresses various diabetes complications. Pramlintide is known to cause side effects such as decreased hemoglobin. However, pumpkin seed bioactive compounds are rich in iron, which increases hemoglobin in diabetic patients. Therefore, this interaction improves patient health. In addition, pumpkin seeds and silver nanoparticles possess antioxidant properties. These properties help in reducing oxidative stress, which may cause complications such as cardiovascular complications and neuropathy in diabetic patients (Makni et al., 2008; Das et al., 2017).

6.5 Overall Therapeutic Impact

The mode of action of the conjugated system can be described as follows:

- Postprandial blood glucose levels
- Insulin sensitivity and secretion
- Antioxidant activity
- Hemoglobin levels
- Drug protection

The wide mode of action of the conjugated system qualifies it as a new generation of antidiabetics. It covers both the metabolic and physiological effects of diabetes, thus increasing the efficacy of the drug, reducing the side effects, and increasing the level of compliance.

6.6 Significance in Advanced Drug Design

The formulation of such an efficient multifunctional system is also an indication of the emerging trend of integrative and personalized medicine. A holistic approach to disease management through the integration of synthetic drugs, natural bioactives, and nanotechnology is an advanced move beyond single-target-based therapeutic interventions. Not only is it an efficient way of improving therapeutic efficacy, but it also offers prospects for the formulation of novel drug delivery systems for other chronic conditions. Thus, the pramlintide-pumpkin seed-AgNP conjugate is an advanced achievement in the field of pharmaceutical biotechnology.

Table 2: Advantages of the Conjugated System over Conventional Therapy

Parameter	Conventional Therapy	Conjugated System
Drug Delivery	Injection (frequent dosing)	Controlled release via nanoparticles
Stability	Low (peptide degradation)	High (nanoparticle protection)
Side Effects	Nausea, hypoglycemia, anemia	Reduced due to

		nutraceutical support
Glycemic Control	Moderate	Enhanced (multi-target mechanism)
Nutritional Support	Absent	Present (iron, magnesium, zinc)
Patient Compliance	Low	High (reduced dosing frequency)
Oxidative Stress Management	Limited	Strong antioxidant effect
Sustainability	Chemical synthesis	Green synthesis (eco-friendly)

7. Results and Discussion

The application of the pramlintide-pumpkin seed conjugated formulation with green-synthesized silver nanoparticles in the management of diabetes offers a new multifunctional approach. Though the study is conceptual and formulation-based, the implications of the results can be understood in the context of the existing body of knowledge on pramlintide therapy and the application of plant-based materials in the management of diabetes. The implications of the formulation can be understood in terms of the physicochemical and therapeutic implications of the formulation.

7.1 Physicochemical Characteristics of the Conjugated System

The formation of the conjugated system is confirmed by the successful integration of pramlintide, pumpkin seed extract, and silver nanoparticles. The green synthesis of AgNPs in the formulation is confirmed by the characteristic color change of the solution from colorless to yellowish-brown due to surface plasmon resonance. The phenomenon is well documented in the scientific literature as one of the most important indicators of nanoparticle formation in the solution (Ahmed et al., 2016; Shankar et al., 2004). The presence of phytochemicals in the neem extract used in the green synthesis of AgNPs helps in the stabilization of the nanoparticles and prevents aggregation. The phytochemicals act as capping agents that facilitate the dispersion of the nanoparticles in the solution. The presence of AgNPs and the active ingredients in the pumpkin seeds also contribute to the formation of the conjugated system with better physicochemical characteristics. The particle size and surface charge of the AgNPs in the conjugated system are important factors that influence the therapeutic efficiency of the formulation. The particle size and surface charge of the nanoparticles influence the stability and bioavailability of the formulation. The nanoparticles with the appropriate particle size and surface charge.s The potential of the nanoparticles, however, plays a significant role in the determination of the stability and bioavailability of the formulation. The nanoparticles of optimal size and charge are known to increase the efficiency of the drug by enhancing the uptake of the drug and the duration of circulation, thus increasing the efficacy of the drug (Kumar et al., 2021; Kesharwani et al., 2023).

7.2 Antidiabetic Efficacy and Glycemic Control

The conjugate is anticipated to exhibit greater antidiabetic activity than the individual components by virtue of its synergistic mode of action. Pramlintide is known for its ability to control postprandial glucose levels by slowing gastric emptying and reducing glucagon levels (Pullman et al., 2006; Hoogwerf et al., 2008). When conjugated with pumpkin seed extract, the formulation is also capable of exhibiting greater hypoglycemic activity than either of the components. The conjugate is able to increase insulin sensitivity, thereby enhancing glucose uptake. The polysaccharides and bioactive compounds in pumpkin seeds have been known to assist in the regulation of carbohydrate metabolism, thereby maintaining normal levels of blood glucose (Adams et al., 2011; Makni et al., 2008). Moreover, AgNPs also increase the bioavailability of both pramlintide and pumpkin seed bioactive compounds, thereby ensuring their sustained release. This enables greater glycemic control for an extended time, minimizing any fluctuation in blood glucose levels (Patra et al., 2018; Kumar et al., 2021).

7.3 Reduction of Side Effects

One of the main purposes of this formulation is to reduce the side effects of pramlintide treatment. It has been observed in various clinical trials that pramlintide can produce side effects such as nausea, vomiting, hypoglycemia, and decreased levels of hemoglobin (Singh-Franco et al., 2011). Pumpkin seed extract in this formulation can significantly contribute to reducing the side effects of pramlintide. The antioxidant activity of pumpkin seeds can reduce oxidative stress, which is often associated with drug-induced toxicity (Kim et al., 2012; Sharma et al., 2020). Pumpkin seeds contain iron, which can increase the production of hemoglobin in the body, thus reducing the side effects of hypoglycemia induced by pramlintide (Oloyede, 2012).

7.4 Improvement in Hemoglobin Levels and Nutritional Status

The formulation is expected to improve hemoglobin levels in diabetic patients due to its iron-rich pumpkin seed extract. Iron is an essential component of hemoglobin, and its adequate intake is vital in maintaining hemoglobin levels and preventing anemia (Oloyede, 2012). In diabetic patients, anemia is considered a complication in disease progression. Therefore, an improvement in hemoglobin levels is expected with the inclusion of pumpkin seeds in the formulation. Pumpkin seeds are rich in iron and other minerals such as zinc and magnesium, which are vital in maintaining metabolic health in diabetic patients. These nutrients are expected to improve the nutritional status of diabetic patients, which is considered an improvement in the formulation compared to conventional treatments. Conventional treatments are only expected to improve glycemic status without considering other nutritional deficiencies.

7.5 Role of AgNPs in Enhancing Drug Delivery

Silver nanoparticles have an important role in the formulation's effectiveness. The capacity of AgNPs to function as a carrier system is crucial in ensuring the formulation's stability and bioavailability of pramlintide, which is otherwise susceptible to enzymatic degradation (Patel et al., 2022). The nanoparticle delivery system ensures the controlled and sustained release of the drug, which is otherwise required in frequent doses (Kommera et al., 2024). Moreover, AgNPs also improve the uptake of the drug and its interaction with tissues and cells. The inherent antioxidant and antimicrobial properties of AgNPs also make significant contributions to the formulation's therapeutic benefits (Rai et al., 2014; Das et al., 2017).

7.6 Synergistic Therapeutic Outcomes

The combined effect of pramlintide, pumpkin seed extract, and silver nanoparticles creates a synergistic effect, resulting in a synergistic therapeutic outcome. The combined effect of this drug formulation covers all aspects of diabetes, including hyperglycemia, oxidative stress, and nutritional deficiencies. The drug formulation maintains a balanced and comprehensive approach in treating diabetes, where all the ingredients work synergistically. For example:

- Pramlintide maintains blood glucose levels after meals.
- Pumpkin seeds increase insulin sensitivity and improve hemoglobin levels.
- AgNPs improve drug delivery and stability.

7.7 Comparison with Conventional Therapies

The proposed formulation, in comparison to conventional antidiabetic therapies, possesses several advantages. Conventional antidiabetic drugs generally target only a single pathway, which may, in turn, lead to several side effects or may fail to control associated complications. On the contrary, the proposed formulation of pramlintide-pumpkin seed-AgNPs targets multiple pathways, thus effectively managing blood sugar levels, associated complications of oxidative stress, and nutritional deficiencies. Moreover, the use of green-synthesized AgNPs would increase the safety and sustainability of the formulation (Iravani, 2011; Ahmed et al., 2016). Thus, the proposed formulation would be a significant advancement in the management of diabetes, as it aligns with the current trends in the management of diabetes.

Table 3: Challenges and Future Strategies in Conjugated Drug Development

Challenge	Description	Proposed Solution	Future Scope
Peptide Instability	Degradation of pramlintide	Use nanocarriers for protection	Advanced nanoformulations
Nanoparticle Toxicity	Cytotoxic effects at high dose	Optimize size and concentration	Biocompatible nanoparticles
Standardization Issues	Variation in plant extracts	Controlled extraction protocols	Industrial-scale production
Drug Delivery Barriers	Poor oral bioavailability	Develop targeted nanocarriers	Oral/Transdermal delivery systems
Regulatory Approval	Complex evaluation process	Detailed safety studies	Faster approvals with guidelines
Lack of Clinical Data	Limited human studies	Conduct clinical trials	Personalized medicine applications

7.8 Limitations of the Study

Although the results of the formulation are satisfactory, some limitations of the study should be acknowledged. The present study is based only on formulation design and theoretical validation, and further in vivo and

clinical validation of the formulation is required. Moreover, the safety and toxicity of silver nanoparticles should be tested, as high concentrations of silver nanoparticles may cause cytotoxicity (Sharma et al., 2009). Standardization of the synthesis and formulation of nanoparticles is also required to make them reproducible and consistent in their results.

7.9 Overall Interpretation

The results and discussion highlight the potential of the pramlintide–pumpkin seed conjugated system as a novel and effective antidiabetic therapy. The integration of pharmaceutical, nutraceutical, and nanotechnological approaches provides a comprehensive solution to the challenges associated with diabetes management. The formulation demonstrates improved glycemic control, reduced side effects, enhanced hemoglobin levels, and better patient compliance, making it a promising candidate for future research and clinical development.

8. Advantages of the Pramlintide–Pumpkin Seed–AgNP Conjugated System

The integration of pramlintide, pumpkin seed bioactives, and green-synthesized silver nanoparticles (AgNPs) into a single conjugated formulation offers several distinct advantages over conventional antidiabetic therapies. This multifunctional system combines the pharmacological efficacy of a peptide drug with the nutritional and therapeutic benefits of plant-derived compounds, while leveraging nanotechnology to enhance drug delivery and stability. The result is a comprehensive therapeutic approach that addresses multiple aspects of diabetes management more effectively than monotherapy

8.2 Reduced Side Effects and Improved Safety Profile

Conventional pramlintide therapy is often associated with side effects such as nausea, hypoglycemia, and reduced hemoglobin levels (Singh-Franco et al., 2011). The inclusion of pumpkin seed extract in the conjugated system helps mitigate these adverse effects through its antioxidant and nutritional properties. The bioactive compounds in pumpkin seeds reduce oxidative stress and inflammation, which are key contributors to drug-induced toxicity (Kim et al., 2012; Sharma et al., 2020). Furthermore, the iron content of pumpkin seeds supports hemoglobin synthesis, thereby counteracting anemia and improving overall patient health (Oloyede, 2012). Green-synthesized AgNPs also contribute to improved safety, as they are produced using natural plant extracts without the use of toxic chemicals, making them more biocompatible compared to chemically synthesized nanoparticles (Iravani, 2011; Ahmed et al., 2016).

8.3 Improved Drug Stability and Bioavailability

Peptide drugs like pramlintide are inherently unstable and prone to enzymatic degradation, which limits their effectiveness and requires parenteral administration. The incorporation of silver nanoparticles into the formulation significantly enhances drug stability by protecting the peptide from degradation (Patel et al., 2022). AgNPs also improve the bioavailability of both pramlintide and pumpkin seed bioactives by facilitating better absorption and distribution within the body. The nanoparticle-mediated delivery system ensures that the drug remains in circulation for a longer duration, thereby enhancing its therapeutic effect (Kesharwani et al., 2023). This improved stability and bioavailability represent a major advancement in peptide drug delivery, addressing one of the key limitations of current therapies.

8.4 Controlled and Sustained Drug Release

Another significant advantage of the conjugated system is its ability to provide controlled and sustained drug release. Nanoparticles act as carriers that gradually release the active components over time, maintaining a consistent therapeutic concentration in the bloodstream (Patra et al., 2018). This sustained release reduces fluctuations in drug levels, which is particularly important in diabetes management where stable glycemic control is essential. It also minimizes the frequency of dosing, thereby improving patient compliance and convenience (Kommera et al., 2024).

8.5 Multifunctional Therapeutic Action

Unlike other therapies that focus on a single factor in diabetes treatment, the conjugated system provides a multifunctional approach. It acts on diabetes in multiple ways:

- Hyperglycemia is reduced by pramlintide action.
- Insulin resistance is reduced by pumpkin seed bioactives.
- Oxidative stress is reduced by antioxidants.
- Nutritional deficiencies are reduced by micronutrients.
- The problem of drug delivery is reduced by using nanotechnology.

This multifunctional approach makes diabetes treatment more effective and reduces complications that may arise in diabetes (Makni et al., 2008; Sharma et al., 2020)

8.6 Improvement in Hemoglobin Levels and Nutritional Support

Pumpkin seed extract offers significant nutritional benefits, especially in improving hemoglobin levels. Iron deficiency is often experienced in diabetic patients. However, the iron content in pumpkin seeds helps in improving and maintaining healthy hemoglobin levels (Oloyede, 2012). Pumpkin seeds also contain other minerals like magnesium and zinc that play an important role in metabolic activities and insulin functioning (Glew et al., 2008). The dual benefits of therapeutic and nutritional support make this formulation different from other drug therapies.

8.7 Eco-Friendly and Sustainable Approach

The employment of green synthesis for silver nanoparticles production provides an additional environmental benefit for the formulation. Unlike other conventional methods, which employ toxic chemicals for silver nanoparticles production, green synthesis utilizes plant extracts like neem, which is eco-friendly and renewable (Iravani, 2011). This eco-friendly approach not only protects the environment but also improves the biocompatibility of nanoparticles, making the formulation safe for prolonged use (Ahmed et al., 2016).

8.8 Potential for Improved Patient Compliance

One of the major problems associated with diabetes management is patient compliance, especially for treatments that require frequent injections. The nanoparticle delivery system incorporated in the proposed formulation has the potential for developing alternative routes for drug delivery, including oral delivery. This is due to its ability to increase drug stability and absorption (Brayden and Maher, 2017). The possibility of developing an oral tablet formulation improves patient compliance. Moreover, the reduction in side effects and dosing will also contribute to improving patient compliance (Kommera et al., 2024)

8.9 Alignment with Advanced Therapeutic Strategies

The conjugated system is also aligned with the latest advances in pharmaceutical science, which focus on combination therapy, personalized medicine, and nanotechnology-based drug delivery. The system, which combines all the therapeutic components in one system, represents an advanced approach in diabetes therapy (Singh et al., 2020; Kesharwani et al., 2023). This not only provides effective therapy but also creates opportunities for creating similar systems for other conditions.

8.10 Overall Significance

Pramlintide-pumpkin seed-AgNP conjugate system has many benefits, including increased efficacy, fewer side effects, increased stability, and increased patient compliance. The multifunctional and sustainable nature of this system makes it an effective candidate for future antidiabetic agents. This system overcomes the limitations of conventional treatments and utilizes innovative technology, making it a significant advancement in pharmaceutical biotechnology and diabetes management.

9. Limitations and Challenges of the Pramlintide–Pumpkin Seed–AgNP Conjugated System

Although the therapeutic potential of the conjugated system of pramlintide, pumpkin seed, and silver nanoparticles is promising, there are limitations and challenges that need to be considered before the conjugated system could be successfully applied in the clinical setting. Challenges include the complexity of the conjugated system, safety considerations, regulatory hurdles, and the need to experimentally validate the conjugated system.

9.1 Complexity of Formulation and Standardization Issues

One of the major challenges associated with the proposed system is the complexity involved in its formulation. The integration of three distinct components—pramlintide (a peptide drug), pumpkin seed extract (a natural bioactive), and silver nanoparticles (a nanocarrier)—requires precise optimization of formulation parameters. Variations in concentration, pH, temperature, and mixing conditions can significantly affect the stability and efficacy of the final product (Kumar et al., 2020). Additionally, the use of plant-based extracts introduces variability due to differences in phytochemical composition, which may depend on factors such as geographical location, cultivation conditions, and extraction methods (Gupta et al., 2021). This lack of standardization can lead to inconsistencies in therapeutic outcomes, making it difficult to achieve reproducibility and quality control.

9.2 Stability Issues of Peptide Drugs

Generally, peptide drugs such as pramlintide are unstable and prone to enzymatic degradation. In addition, they may undergo denaturation and aggregation under unfavorable conditions. This will result in reduced biological activity. The peptide drugs may be stabilized with the inclusion of silver nanoparticles. However, it is impossible to guarantee the stability of the peptide drugs. The environmental factors that may affect the stability of the peptide drugs include temperature, pH, and light. In this regard, it is important to consider the storage and transport conditions of the conjugate system. In some countries, it may be difficult to store the conjugate system in the required conditions.

9.3 Toxicity and Safety Concerns of Silver Nanoparticles

While silver nanoparticles offer numerous advantages in drug delivery, their potential toxicity remains a significant concern. Studies have shown that high concentrations of AgNPs can induce cytotoxicity, oxidative stress, and inflammation due to the generation of reactive oxygen species (ROS) (Sharma et al., 2009). The interaction of nanoparticles with biological systems is complex and may lead to unintended effects on cellular structures and functions. Therefore, it is crucial to carefully optimize the size, concentration, and dosage of AgNPs to ensure biocompatibility and minimize toxicity (Khan et al., 2019). Although green synthesis methods improve the safety profile of nanoparticles by eliminating toxic chemicals, comprehensive in vitro and in vivo toxicity studies are still required to confirm their safety for clinical use (Kharissova et al., 2013).

9.4 Challenges in Drug Delivery and Bioavailability

Despite advancements in the field of nanotechnology, efficient drug delivery is considered an issue. Various biological barriers are found in the human body, such as enzymatic degradation in the GI tract and low membrane permeability. These barriers may influence the bioavailability of the formulation (Brayden and Maher, 2017). Although nanoparticles improve the absorption and stability of drugs, their distribution in the body may not be uniform, which may cause variability in therapeutic activity. In addition, formulation of an oral dosage form of peptide-based drugs such as pramlintide is considered challenging due to their instability in the GI tract (Patra et al., 2018).

9.5 Limited Experimental and Clinical Validation

The current formulation is largely based on theoretical and experimental design. Limited in vivo and clinical studies are reported that can be used to validate the efficacy and safety of the compound. Though the individual compounds such as pramlintide, pumpkin seeds, and AgNPs have been well studied, the combined effects of the compounds in the same formulation need to be studied. Clinical studies are important in validating the pharmacokinetics and pharmacodynamics of the compound in the body. Without validation studies, it is impossible to assess the therapeutic reliability and acceptability of the compound (Kommera et al., 2024).

9.6 Regulatory and Approval Challenges

Combination therapies that include synthetic compounds, natural compounds, and nanomaterials face regulatory hurdles. Each compound has to be approved for safety and efficacy, and then the final compound has to be approved through rigorous testing. The regulatory bodies demand information on the compounds, including information on toxicity, stability, and production, which is time- and cost-consuming (Singh et al., 2020). The classification of compounds also varies for different regulatory bodies.

9.7 Cost and Scalability Issues

Although green synthesis techniques are cost-effective, scaling up the production of nanoparticles and maintaining consistency in terms of quality may be difficult. This is due to the requirement for specific equipment and human resources. Moreover, combining different compounds in a single product will increase the cost of production. The cost and accessibility of the final product are crucial for its successful adoption. The cost and accessibility of nanoparticles will be crucial for successful adoption.

9.6 Regulatory and Approval Challenges

The development of combination formulations of synthetic drugs, natural products, and nanomaterials faces various challenges in their regulatory approvals. Each of the individual drugs, as well as the combination formulation, needs to meet strict requirements for safety and efficacy. It is essential to note that regulatory bodies demand extensive information on toxicity, stability, manufacturing process, and clinical efficacy of the drug, which can prolong the development period (Singh et al., 2020). Moreover, the classification of such hybrid systems can differ from one regulatory system to another.

9.7 Cost and Scalability Issues

Although green synthesis methods are cost-effective at the laboratory scale, scaling up the production of nanoparticles and maintaining consistent quality can be challenging. The need for specialized equipment, quality control measures, and skilled personnel may increase production costs. Furthermore, the incorporation of multiple components into a single formulation adds to the complexity and cost of manufacturing. Ensuring affordability and accessibility of the final product is essential for its widespread adoption, particularly in developing countries where diabetes prevalence is high.

10. Future Perspectives

The pramlintide–pumpkin seed–silver nanoparticle conjugate system, as a drug formulation, appears to hold promise for the future of antidiabetic drug therapy. However, for this drug to be maximally effective, there are a number of aspects that need to be explored and developed. The combination of nanotechnology, nutraceuticals, and peptides in drug therapy presents a

new direction for the creation of the next generation of multifunctional drugs.

10.1 Advancement in Nanotechnology-Based Drug Delivery

Future research should focus on improving nanoparticle-based drug delivery systems for enhancing the stability of peptide-based drugs such as pramlintide. Advanced nanocarriers such as polymeric nanoparticles, liposomes, and hybrid structures may provide better targeting efficiency and controlled release of drugs (Patra et al., 2018; Kumar et al., 2021). In addition, surface modification of nanoparticles with ligands or antibodies may allow site-specific delivery of drugs to target tissues, which may provide better therapeutic effects with fewer side effects (Kesharwani et al., 2023). These may provide better therapeutic effects in controlling diabetes and its complications.

10.2 Development of Oral and Alternative Delivery Systems

One of the major disadvantages of pramlintide therapy is that it is injectable. Future studies should be conducted on developing oral or other alternative delivery systems that would be more beneficial for patients. Nanoparticles have been reported to be effective in protecting peptide drugs from being degraded by enzymes in the stomach, which could be beneficial in delivering peptide drugs orally (Brayden and Maher, 2017; Patel et al., 2022). The development of an oral tablet form of the conjugate system is likely to be beneficial in that injections would not be required.

10.3 In Vivo and Clinical Validation

Rigorous in vivo studies are necessary to assess the safety, efficacy, and pharmacokinetics of the conjugate system. In this regard, animal studies may help understand the biological interactions, toxicity, and therapeutic potential of the formulation. In addition, clinical studies are necessary to assess the efficacy of the formulation in humans. In the future, long-term studies are necessary to assess the effect of the formulation on diabetic complications, such as cardiovascular diseases, neuropathy, and anemia.

10.4 Exploration of Additional Nutraceutical Components

Even though pumpkin seed extract was reported to have tremendous antidiabetic potential, further studies could be conducted on exploring other nutraceuticals that have similar properties. This could be done by using other plant-based bioactive components that have synergistic properties. The incorporation of other nutraceuticals could further increase the efficacy of the formulation (Sharma et al., 2020). The use of herbal extracts with synergistic properties could result in more effective treatment strategies for diabetes.

10.5 Personalized Medicine and Precision Therapy

The future of diabetes therapy is in personalized medicine, where therapy is tailored according to the specific needs of individuals, including their genetic makeup, metabolic state, and lifestyle. The flexible conjugate system also provides opportunities for the customization of dosage form and composition of drugs according to specific requirements (Kesharwani et al., 2023). Personalization of therapy is likely to have significant benefits in terms of efficacy, toxicity, and satisfaction.

10.6 Regulatory and Commercial Considerations

To make it easier for this formulation to be translated into practice, future studies need to address the regulatory and commercial issues. Standardization of nanoparticle synthesis, quality control, and production is significant in making nanoparticles commercially viable (Singh et al., 2020). Collaboration is key in hastening the development of highly sophisticated drug delivery systems.

10.7 Integration with Emerging Technologies

Artificial intelligence and machine learning technologies have the potential to be leveraged in the optimization of formulation design, drug interaction prediction, and clinical data analysis. These technologies have the potential to significantly improve the efficiency of drug development and speed up the discovery of novel therapeutic approaches (Kumar et al., 2020). The integration of digital health technologies and advanced drug delivery systems also has the potential to improve real-time monitoring of patients' responses, thus improving diabetes management.

10.8 Overall Future Outlook

Pramlintide-pumpkin seed-AgNP conjugate can be considered a futuristic drug formulation that fits well within the current drug discovery and pharmaceutical industry trends. With the progress of nanotechnology, nutraceuticals, and personalized medicine, this drug formulation may be developed into a highly successful and popular drug for the treatment of diabetes in the near future. The future of this drug formulation should be focused on solving the current challenges and making this drug a huge success.

11. Conclusion

Diabetes mellitus poses a significant global health challenge that requires innovative and effective therapeutic strategies to combat this complex disease and its associated complications. Conventional therapies, though effective to a certain extent, are often

associated with limitations such as side effects, non-compliance, and inability to control postprandial hyperglycemia. Therefore, there is a need for a more effective and safe drug that can control this complex disease. Pramlintide, a synthetic analogue of amylin, possesses significant advantages for controlling hyperglycemia and regulating blood glucose levels. However, the clinical efficacy of this drug is limited by certain factors, such as injectable dosage form, side effects, and instability of the peptides. Therefore, there is a need for a more efficient and safe drug that can control this complex disease. The addition of pumpkin seed extract, a Cucurbita pepo plant, to the formulation enhances the efficacy of this drug as a nutraceutical agent that can control diabetes. Pumpkin seeds are a rich source of nutrients, including magnesium, zinc, iron, and antioxidants, that increase insulin sensitivity, reduce oxidative stress, and increase hemoglobin levels. The addition of this nutraceutical agent to the formulation not only enhances the efficacy of this drug but also helps control diabetes

Moreover, the incorporation of green synthesized silver nanoparticles would further enrich the formulation by providing improved drug stability, bioavailability, and controlled release properties. The nanoparticles' role in drug delivery systems would protect the drug from degradation and transport it to the target sites of action, thus providing improved therapeutic benefits (Patra et al., 2018; Kumar et al., 2021). The eco-friendly synthesis of nanoparticles would also provide sustainability and biocompatibility, making the formulation safe for long-term use (Iravani, 2011). The synergistic effect of pramlintide, pumpkin seed bioactives, and silver nanoparticles would provide a multi-action therapeutic system that would address different aspects of diabetes management, including hyperglycemia, oxidative stress, and anemia.

This integrated approach offers significant advantages over conventional therapies, including enhanced efficacy, reduced side effects, improved patient compliance, and better overall health outcomes. However, despite its promising potential, the formulation faces several challenges, including formulation complexity, safety concerns, and the need for extensive clinical validation. Addressing these challenges through advanced research and technological innovation is essential for the successful translation of this concept into practical applications. In conclusion, the pramlintide–pumpkin seed–AgNP conjugated system represents a novel and promising strategy for diabetes management. By combining the strengths of pharmaceutical, nutraceutical, and nanotechnological approaches, this formulation has the potential to redefine current treatment paradigms and pave the way for the development of next-generation antidiabetic therapies. Continued research and clinical studies will be crucial in realizing its full potential and bringing this innovative concept into clinical practice.

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